

Applicants : Samuel J. Danishefsky and Bishan Zhou
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REMARKS

Claims 1-17, 33-49 and 84-91 were pending in the subject application. By this Amendment, applicants have amended claims 1, 2, 3, 8, 14, 33, 34, 35, 40, 46, 84, 85, 86, 90 and 91. Applicants have also added claim 121. Therefore, claims 1-17, 33-49, 84-91 and 121 are currently pending in this application.

Support for the amendment to claim 1 may be found, *inter alia*, in the specification, as originally filed, on page 3, lines 19-33, on page 10, lines 2 and 20-23 and on page 24, line 24.

Support for the amendment to claim 3 may be found, *inter alia*, in the specification, as originally filed, on page 9, line 16.

Support for the amendment to claim 3 may be found, *inter alia*, in the specification, as originally filed, on page 9, line 35.

Support for the amendment to claim 8, may be found, *inter alia*, in the specification, as originally filed, on page 10, lines 20-23.

Support for the amendment to claim 14, may be found, *inter alia*, in the specification, as originally filed, on page 10, lines 7-9.

Support for the amendment to claim 33, may be found, *inter alia*, in the specification, as originally filed, on page 10, line 2, on page 15, lines 3-6, on page 24, line 24, on page 38, compounds 46 and 49, on page 40, compound 63 and on page 42, compound 81.

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Support for the amendment to claim 34, may be found, *inter alia*, in the specification, as originally filed, on page 13, line 26.

Support for the amendment to claim 35, may be found, *inter alia*, in the specification, as originally filed, on page 14, line 18.

Support for the amendment to claim 40, may be found, *inter alia*, in the specification, as originally filed, on page 15, lines 3-6.

Support for the amendment to claim 46, may be found, *inter alia*, in the specification, as originally filed, on page 14, lines 26-27.

Support for the amendment to claim 84, may be found, *inter alia*, in the specification, as originally filed, on page 10, lines 20-23, on page 39, compounds 47, 48 and 55 and on page 55, compound 107.

Support for the amendment to claim 85, may be found, *inter alia*, in the specification, as originally filed, on page 25, lines 24-25.

Support for the amendment to claim 86, may be found, *inter alia*, in the specification, as originally filed, on page 26, lines 20-21.

Support for the amendment to claim 87, may be found, *inter*

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alia, in the specification, as originally filed, on page 26, lines 23-25.

Support for the amendment to claim 90, may be found, *inter alia*, in the specification, as originally filed, on page 26, lines 27-29.

Support for the amendment to claim 91, may be found, *inter alia*, in the specification, as originally filed, on page 26, lines 31-33.

Support for new claim 121, may be found, *inter alia*, in the specification, as originally filed, on page 24, lines 19-34 and on page 55, compounds 104 and 107.

Rejection under 35 U.S.C. § 112, second paragraph

On pages 2-3 of the May 5, 2004 Office Action, the Examiner rejected claims 1-4, 12, 14-17, 33-36, 44, 46-49, 84-86, and 88 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Reason 1

The Examiner alleged that the intended scope of "acyl" for the various R groups is completely unknown, other than the three moieties described for R₃ in the specification on page 3. The Examiner further alleged that the term "acyl" is too broad as it encompasses moieties such as phosphonyl, sulfonyl, and other non-carbonyl derived groups with any type of atom in a chain or ring attached thereto. The Examiner also alleged that

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the examples given for the acyl term are exemplified in acyloxy moieties.

In response, applicants amended claims 1, 33 and 84 to recite "C(O)(C₁-C₄ alkyl)". Consequently, the rejection of indefiniteness does not apply to the amended claims and should be withdrawn.

Reason 2

The Examiner also alleged that various terms in the specification are not well-defined and that applicants are not clearly defining their invention. In particular, the Examiner alleged that the terms "ether," "ester," "amide," "aromatic," "substituted phthalimide" and "sulfide group" require proper definition. The Examiner alleged the term "sulfide group" is open-ended since sulfur is divalent and so, an additional moiety has to be defined for it. The Examiner raised similar objection to terms for the classes of compounds such as "carboxylic esters," "sulfonamide system," "aryl system" and "heteroaryl system" alleging that they require definition and further questioned how these groups are attached at the various ring positions in the claimed compounds and whether they can be substituted and with what type of groups.

In response, applicants amended claims 1, 33 and 84 to recite either "O(C₁-C₄ alkyl)" or "O(C₁-C₆ alkyl)". Applicants also amended the claims to recite "(C₁-C₅) alkyl" or "benzyl" groups.

However, applicants have maintained the term "aromatic" and contend that this term is well-defined and understood in the

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literature. For example, applicants direct the Examiner's attention to pages 604-607 in Streitweiser et al., Introduction to Organic Chemistry, 4th Ed., 1992, for a general description of "aromatic." (**Exhibit 1**).

Reason 3

The Examiner also alleged that claims 14 and 46 contain the extraneous text, i.e. "[[3]]" appearing after "benzene".

In response, applicants have amended claims 14 and 46 to recite "benzyl". As noted above, support for these amendments may be found on page 10, lines 7-9 and page 14, lines 26-27.

Accordingly the applicants request that the Examiner withdraw the rejection of claims 1-4, 14-17, 33-36, 44, 46-49, 84-86 and 88 under 35 U.S.C. § 112, second paragraph, on the basis that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Objections under 37 CFR 1.75 (c)

On page 3 of the May 5, 2004 Office Action, the Examiner objected to claims 3-17 and 35-49 and 86-91 under 37 CFR 1.75 (c) as allegedly being in improper form because a multiple dependent claim cannot refer to two sets of claims to different features, citing MPEP § 608.01 (n). The Examiner alleged that the improper dependency appears in each of claims 3, 35 and 86 and that the remaining claims objected to herein are dependent on these claims.

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In response, applicants have amended claim 2 to define R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , and R_9 . Applicants have also amended claim 3 to define R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 . Claims 34-35 and 85-86 have been similarly amended. Accordingly, the applicants request that the Examiner withdraw the objection to claims 3-17 and 35-49 and 86-91 under 37 CFR 1.75 (c) on the basis they are in improper form.

On page 3 of the May 5, 2004 Office Action, the Examiner also objected to claims 5-9, 14, 37-39, 41, 46, 87, 89 and 91 under 37 CFR 1.75 (c), as allegedly being in improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner alleged that the applicant is required to cancel the claim(s), or amend the claims(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The Examiner further alleged that these claims recite subject matter outside the scope of claims from which they depend. The Examiner alleged that claims 14 and 46 recite R_4 as benzene and that this is outside the scope of the main claims. The Examiner also alleged that the remaining claims values for R_2 which are recited are also outside the scope for main claims which recite ethers, esters, amide, aromatics, phthalimides but not H, OH, formyl or keto groups.

In response, applicants have amended claims 1-3 to recite "wherein R_2 is H, OH, $O(C_1-C_4 \text{ alkyl})$, O-benzyl, $OC(O)H$, $OC(O)(C_1-C_6 \text{ alkyl})$, $OC(O)\text{benzyl}$, $OSi(CH_3)_2(t\text{-butyl})$, or a phthalimide group." Support for the addition of H and OH may be found as noted above on page 10, lines 20-23 of the subject application which recites "In all of the embodiments, and particularly in the preferred embodiments, R_2 is $OC(O)H$, R_2 is

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H, R₂ is OH, R₂ is -O-benzene, R₂ is OCOCH₃, R₂ is -O-t-butyltrimethylsilyl, or R₂ is -O-Pivaloyl." Claims 5-9, through their dependency on claims 1-3, recite values for R₂ that limit the scope of the claims upon which they depend. For example, claim 5 recites "wherein R₂ is OC(O)H". Likewise, claims 6-9, 14, 37-39, 41, 46, 87, 89 and 91 all further limit the scope of R groups of the independent claims upon which they depend. Accordingly, the applicants request that the Examiner withdraw the objection to claims 5-9, 14, 37-39, 41, 46, 87, 89 and 91 under 37 CFR 1.75 (c), as allegedly being in improper dependent form for failing to further limit the subject matter of a previous claim.

On page 4 of the May 5, 2004 Office Action, the Examiner also objected to the specification as allegedly failing to provide proper antecedent basis for the claimed subject matter, citing 37 CFR 1.75(d)(1) and MPEP § 608.01(o). The Examiner concluded that correction of R₅ as -OC(2-6)alkyl is required as it is not seen in the specification although the Examiner acknowledged that it was recited in original claim 1.

In response, applicants have amended claims 1 and 33 to recite R₅ as "-OC₍₁₋₆₎ alkyl group". Support for these amendments may be found as noted above on page 10, line 2 (OCH₃) and on page 24, line 24 (-OC₍₂₋₆₎ alkyl group) of the subject application. Support for R₅ as (-OC₍₂₋₆₎ alkyl group) in claim 84 may also be found on page 24, line 24. Accordingly the applicants request that the Examiner withdraw the objection to the specification as allegedly failing to provide proper antecedent basis for the claimed subject matter.

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Rejection under 35 U.S.C. § 112, first paragraph

On page 5 of the May 5 Office Action, the Examiner rejected claims 1-4, 12, 14-17, 33-36, 44, 46-49, 84-86 and 88 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable on skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. The Examiner alleged that the variety of functional groups permitted throughout the R variables is virtually non-limiting for choices such as esters, ethers, amid, aromatics, acyl, substituted, and sulfide groups for which there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share one or more physiological properties urged on p.52 of the specification since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. The Examiner also alleged that the few examples of alkoxy groups, acyloxy, lower acyl and one silyloxy group is not remotely representative of the scope of functional groups permitted at almost every variable, citing *In re Surrey* 151 USPTO 724 regarding sufficiency of disclosure for a Markush group. The Examiner also cited in *In re Wands* cited in MPEP 2164.01(a), August 2000 edition for the criteria for enablement: 1) the breadth of the claims, which the Examiner alleged is easily in the millions; 2) the nature of invention which the Examiner alleged is directed to biological activity and the Examiner also alleged that it is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be

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unpredictable, citing *In re Fisher* 166 USPQ 18; 3) the state of the prior which the Examiner alleged is compounds having the same basic skeleton with identical substitution (referring to the allegedly anticipatory art applied below under the 102(b) rejections) that are used as synthetic precursors; and 4) the lack of direction (i.e. working examples) provided as to what other derivatives might work.

In response, applicants initially point out that the claims have been amended to more clearly define applicants' invention. Applicants further point out that the physiological properties of the claimed invention hinge on the two-tetrahydroisoquinoline aromatic carbon nitrogen framework in the claimed compounds (page 52, lines 6-27). Indeed, compounds with this carbon nitrogen framework have consistently exhibited similar pharmacological, antibiotic, cytotoxic, antitumor, anti-tumorigenic or cellular anti-proliferative properties in vivo and in vitro. Hence, so long as the core tetrahydroisoquinoline structure remains intact, which is the case in applicants' compounds, the type of physiological properties of the claimed compounds would be expected to be similar to the known compounds. Linking established therapeutic or pharmacological utility and those key structural characteristics that induce these physiological properties in a new compound is certainly not unprecedented. Indeed, such correlations have been found acceptable. M.P.E.P. § 2107.01 (III), 4th paragraph, citing *In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (CCPA 1980).

On page 5 of the May 5 Office Action, the Examiner also rejected claims 14 and 46 under 35 U.S.C. § 112, first

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paragraph, as allegedly failing to comply with the written description requirement. The Examiner alleged that the claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner alleged that R4 as benzene recited in the claims 14 and 46 lacks descriptive support in the disclosure originally filed.

In response, as noted above, applicants have amended claims 14 and 46 to recite "benzyl". Support for these amendments may be found on page 10, lines 7-9 and on page 14, lines 26-27

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection of the claims 1-4, 12, 14-17, 33-36, 44, 46-49, 84-86 and 88.

Rejection under 35 U.S.C. § 102

On page 6 of the May 5, 2004 Office Action, the Examiner rejected claims 1-5, 8 and 84-86 under 35 U.S.C. § 102(b) as allegedly anticipated by Zhou, et al., Tetrahedron Lett. 2000, 41, 2043-2046 ("Zhou"). The Examiner alleged that Zhou describes 2 compounds within the instant scope namely 6 and 11 on p.2044 in Scheme 2. The Examiner also alleged that the first compound has a benzyloxy corresponding to instant R2 as an ether group, that compound 11 has a formyl group which corresponds to R2 recited in claim 5 and that the remaining variables in 6 and 11 fall within claims' scope.

In response, applicants point out that the publication date of

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Zhou is March 27 2000. The subject application is a divisional application of U.S Serial No. 09/765,515 and therefore has the same priority date as U.S Serial No. 09/765,515. The filing date of U.S Serial No. 09/765,515 is January 19, 2001. Furthermore, U.S Serial No. 09/765,515 claims priority to U.S Provisional Application No. 60/177,071, filed January 19, 2000.

Claims 1-5 and 8 find support in U.S Provisional Application No. 60/177,071. For example, Zhou's Compound 6 is disclosed on page 20 of U.S Provisional Application No. 60/177,071 and Zhou's compound 11 is disclosed on page 34 of U.S Provisional Application No. 60/177,071. Since the Zhou publication was published after the filing date of U.S Provisional Application No. 60/177,071, it is not prior art against Claims 1-5 and 8.

As to claims 84-86, Zhou does not disclose each and every element of claims 84-86. Specifically, Zhou does not disclose the compounds recited by claims 84-86 where R5 is (-OC₍₂₋₆₎ alkyl group). Since Zhou does not disclose each and every element of claims 84-86, Zhou doesn't anticipate these claims.

Therefore, applicants request that the Examiner withdraw the rejection of claims 1-5, 8 and 84-86 under 35 U.S.C. § 102(b) on the basis that they are anticipated by Zhou.

Rejection under 35 U.S.C. § 103

On pages 6 and 7 of the May 5, 2004 Office Action, the Examiner rejected claims 84-86 under 35 U.S.C. 103(a) as allegedly unpatentable over U.S. Patent Application Publication No. 2003/0008873, published January 9, 2003,

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("Myers"), claiming priority to U.S. Provisional Application 60/245,888, filed November 3, 2000. The Examiner alleged that Myers, applied as of its provisional filing date, teaches very similar compounds to that claimed herein for use in treating cancers citing pages 1-7, especially the compounds on pages 6-7 and the examples such as 3, 6-19. The Examiner alleged that the compounds of Myers have R3 as H and R6 as CN with R2 being a variety of functional groups such as aromatic, amides, ethers and sulfide groups.

The Examiner acknowledged that the sole difference from what is being claimed herein is the presence of an OH vs. instant R9 which can be H, methyl, methoxy, etc. However, the Examiner further alleged that Myers teaches the interchangeability of many groups also claimed herein, citing the definition of X1 on p.3 which includes alkoxy and other choices covering the instant scope. The Examiner concluded that it would have been obvious to one skilled in the art at the time the instant invention was made to modify the compounds pointed out above by changing the substituents on the benzene ring and in so doing obtain instant compounds for use as antitumor agents.

In response, applicants maintain that as amended, claims 84-86 are not obvious in view of Myers. Myers does not disclose any compounds that are species within the genus claimed by the claims 84-86. Specifically, Myers does not disclose examples where R9 is H, CH₃, OCH₃, OC₂H₅, BR, F or CF₃. More importantly, Myers fails to teach how to prepare compounds where R9 is H, CH₃, OCH₃, OC₂H₅, BR, F or CF₃. Myers cites no references that would teach how one would obtain compounds where R9 is H, CH₃, OCH₃, OC₂H₅, BR, F or CF₃.

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Similarly, Myers does not disclose examples of R5 being an (-OC₍₂₋₆₎ alkyl) group, and does not teach how to prepare compounds with R5 being an (-OC₍₂₋₆₎ alkyl) group, and does not cite to a reference that would teach how to obtain compounds with R5 being an (-OC₍₂₋₆₎ alkyl) group. Therefore, one skilled in the art would not be able to prepare the applicants' compounds from the disclosure of Myers.

In view of the foregoing amendments and remarks, applicants request that the Examiner reconsider and withdraw the rejection of claims 84-86 under 35 U.S.C. 103(a).

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A \$110.00 fee for the one-month extension of time is deemed necessary for the filing of this Amendment and a check in that amount is enclosed. No other fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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INTRODUCTION TO ORGANIC CHEMISTRY

FOURTH EDITION

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CHAPTER 21

BENZENE AND THE AROMATIC RING

21.1 Benzene

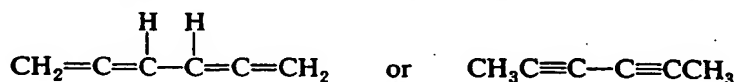
A. The Benzene Enigma

The hydrocarbon now known as benzene was first isolated by Michael Faraday in 1825 from an oily condensate that deposited from illuminating gas. Faraday determined that it has equal numbers of carbons and hydrogens and named the new compound "carbureted hydrogen." In 1834 Mitscherlich found that the same hydrocarbon may be produced by pyrolysis with lime of benzoic acid, which had been isolated from gum benzoin. By vapor density measurements, Mitscherlich established the molecular formula to be C_6H_6 . He named the compound benzin, but other influential chemists protested that this name implied a relationship to alkaloids such as quinine. Finally, the German name benzol, based on the German *öl*, oil, was adopted. In France and England, the name benzene was adopted, to avoid confusion with the typical alcohol ending.

Early in the history of benzene, Laurent proposed the name pheno as we noted in Section 14.7.D. Although the name never gained acceptance, it persists in phenyl, the name of the C_6H_5 group.

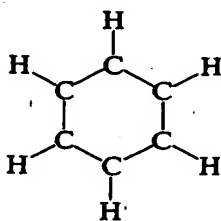
Other preparations of benzene followed these early discoveries, and it was soon recognized that benzene is the parent hydrocarbon of a whole family of organic compounds. The physical properties of benzene (b.p. $80.1^\circ C$, m.p. $5.5^\circ C$) are consistent with its molecular formula of C_6H_6 . For example, cyclohexane, C_6H_{12} , has b.p. $80.7^\circ C$ and m.p. $6.5^\circ C$. A six-carbon saturated alkane would have the formula C_6H_{14} . Therefore, benzene must have four double bonds and/or rings. Yet, it does not exhibit the high reactivity of typical polyenes. In fact, it is remarkably inert to many reagents. For example, it does not react with aqueous potassium permanganate or with bromine water. It does not even react with cold concentrated sulfuric acid. It is stable to air and tolerates free radical initiators.

It may be used as a solvent for Grignard reagents and alkyllithium compounds. All of these properties are totally inconsistent with such C_6H_6 structures as the following.

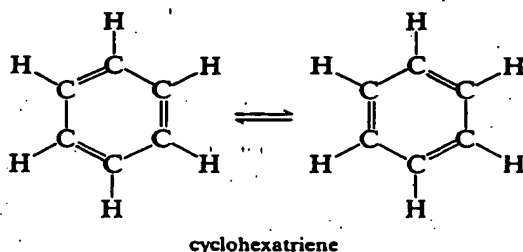


The fact that benzene has a formula that suggests a polyene structure but does not behave at all like other polyenes was a dilemma for nineteenth century chemists. Furthermore, new compounds were continually being discovered that were structurally related to benzene. It was clear that there is something fundamentally different about benzene and its derivatives. As a group, the benzene-like compounds were called aromatic compounds because many of them have characteristic aromas.

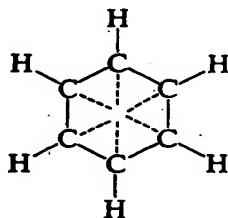
The Kekulé theory of valence, first proposed in 1859, allowed acceptable structures to be written for aliphatic compounds such as ethane and ethylene, but at first it did not appear to be applicable to aromatic compounds. In 1865, Kekulé suggested a regular hexagon structure for benzene with a hydrogen attached at each corner of a hexagonal array of carbons.



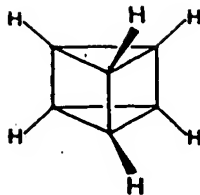
However, this structure violates the tetravalence of carbon inherent in his theory. He later modified his structure to treat benzene as an equilibrating mixture of cyclohexatrienes. However, this structure does not account for the nonolefinic character of benzene.



Other attempts by nineteenth century chemists to explain the benzene problem only emphasize the frustrations inherent in the limited theory of the day. One such example was Armstrong's centroid formula in which the fourth valence of each carbon is directed toward the center of the ring.



Ladenburg, in 1879, proposed an interesting structure that would solve the problem of why benzene displays no polyene properties. In the Ladenburg proposal, benzene was treated as a tetracyclic compound with no double bonds.



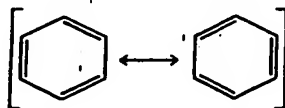
EXERCISE 21.1 The nature of a polycyclic compound as bicyclic, tricyclic, etc., is determined by the number of cuts or bond cleavages required to convert the polycyclic framework to an acyclic chain of atoms. Using this definition, show that the Ladenburg structure is tetracyclic.

Ladenburg's representation of benzene, although not the structure of benzene, is a perfectly valid structure for an organic compound. It has come to be known as "Ladenburg benzene" or "prismane." After considerable effort, prismane was finally synthesized in 1973 by organic chemists at Columbia University. Upon heating to 90 °C, it isomerizes to benzene.

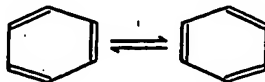
EXERCISE 21.2 Compare a model of prismane with that of benzene. Consider the various isomers of prismane having two different substituents, A and B. Are any of these isomers chiral? Are any of the corresponding disubstituted benzene isomers chiral? How do your answers provide a method by which nineteenth century chemists could have distinguished between the Kekulé and Ladenburg representations of benzene?

Only with the advent of modern wave mechanics did the structure of benzene take its place within a unified electronic theory. The x-ray crystal structure of benzene shows that the compound does indeed have a regular hexagonal structure as Kekulé had originally suggested. The carbon-carbon bond distance of 1.40 Å is intermediate between those for a single bond (1.54 Å) and a double bond (1.33 Å). In a regular hexagon the bond angles are all 120°, and this suggests the involvement of sp^2 -hybrid orbitals. We can now recognize the "fourth valence," which was so difficult for nineteenth century chemists to explain, as being π -bonds from p -orbitals extending equally around the ring, as in Figure 21.1.

In resonance language, we may depict benzene by two equivalent resonance structures.



Note the important difference in meaning between this formulation and that of equilibrating cyclohexatrienes. Cyclohexatriene would have alternating single and double bonds, and the chemical equilibrium between the two alternative structures requires the movement of nuclei.



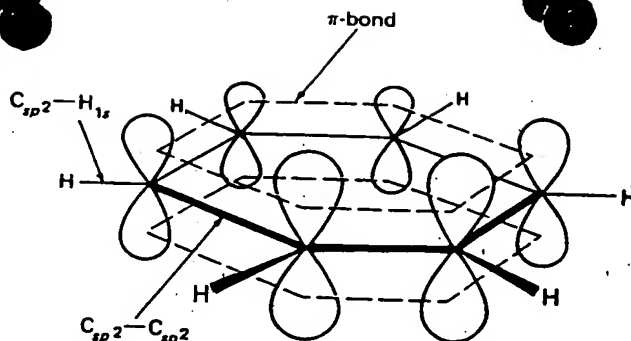
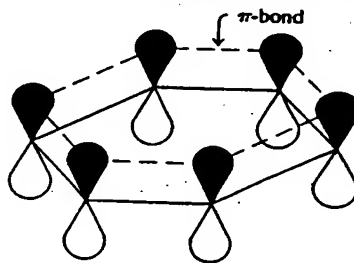
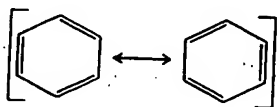


FIGURE 21.1 Orbital structure of benzene.

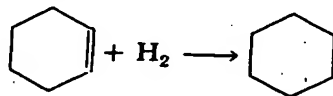
In the resonance structures the carbon-carbon distances remain the same. The resulting resonance hybrid may be written with dotted lines to indicate the partial double-bond character of the benzene bonds.

**Highlight 21.1**

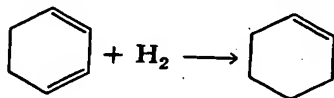
The stability of benzene is its most salient characteristic. Two resonance forms express the equivalent lengths of all double bonds in benzene as does a p -orbital formula.

**B. Resonance Energy of Benzene**

From an examination of the heat of hydrogenation of benzene it is possible to estimate how much more stable benzene is compared to a hypothetical "cyclohexatriene." This imaginary quantity is called the **resonance energy** of benzene. The heat of hydrogenation of the double bond in cyclohexene is $-28.4 \text{ kcal mole}^{-1}$. That for one double bond in 1,3-cyclohexadiene is $-26.5 \text{ kcal mole}^{-1}$.



$$\Delta H^\circ = -28.4 \text{ kcal mole}^{-1}$$



$$\Delta H^\circ = -26.5 \text{ kcal mole}^{-1}$$

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